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Three-Component Synthesis of Methyl 6-Alkyl-3-cyano-2-halopyridine-4-carboxylates

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Abstract—A procedure has been developed for the synthesis of methyl 6-alkyl-3-cyano-2-halopyridine-4-carboxylate by three-component reaction of 4-oxoalkane-1,1,2,2-tetracarbonitriles with hydrogen halides in methanol.

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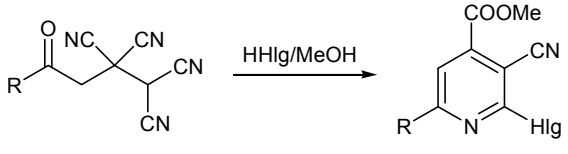
Isonicotinic acid derivatives are widely used in practice, in particular as antitubercular drugs and antidepressants (monoamine oxidase inhibitors). There are published data on bactericidal and other biological activities of isonicotinic acid derivatives [1, 2]. Therefore, development of new methods of synthesis of diffucultly accessible compounds of this series is an important problem. We previously reported that 4-oxoalkane-1,1,2,2-tetracarbonitriles are convenient starting compounds for building up pyridine ring with cyano groups in positions *3* and *4* [3–5].

We have developed a new method for the synthesis of isonicotinic acid derivatives. Three-component synthesis of methyl 6-alkyl-3-cyano-2-halopyridine-4-carboxylates **2a**–**2c** in 76–82% yield has been accomplished by treatment of 4-oxoalkane-1,1,2,2-tetracarbonitriles **1a** and **1b** with hydrogen halides in methanol (Scheme 1).

The structure of **2a**–**2c** was confirmed by IR, ^{1}H NMR, and mass spectra, as well as by ^{13}C NMR and heteronuclear two-dimensional HMBC spectra of **2a**. The IR spectra of **2a**–**2c** contained strong absorption bands at 2231–2235 cm^{-1} due to stretching vibrations of the conjugated cyano group and strong ester carbonyl stretching bands at 1732–1736 cm^{-1}. Compounds **2a**–**2c** showed in the ^{1}H NMR spectra a singlet at 7.95–7.97 ppm from the 3-H proton of the pyridine ring, a singlet at δ 3.94–3.96 ppm from the ester methoxy group, and signals from protons of the corresponding alkyl groups. The isotope ratios of the molecular ion peaks in the mass spectra were 1:3 (**2a**, **2c**) and 1:1 (**2b**).

However, the IR, ^{1}H and ^{13}C NMR, and mass spectral data were insufficient to unambiguously determine the position of the ester group in the pyridine ring of **2a**–**2c**. Therefore, heteronuclear ^{1}H–^{13}C correlation study (HMBC) was performed for compound **2a** (see table). The HMBC spectrum of **2a** displayed a cross-peak between proton in the pyridine ring (δ 7.95 ppm) and ester carbonyl carbon nucleus (C^7, δ_C 162.34 ppm), while no such correlation was observed for the carbon atom of the cyano group (C^9, δ_C 113.91 ppm). These findings indicated that the ester

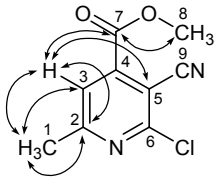
Scheme 1.



1a, **1b** **2a–2c**

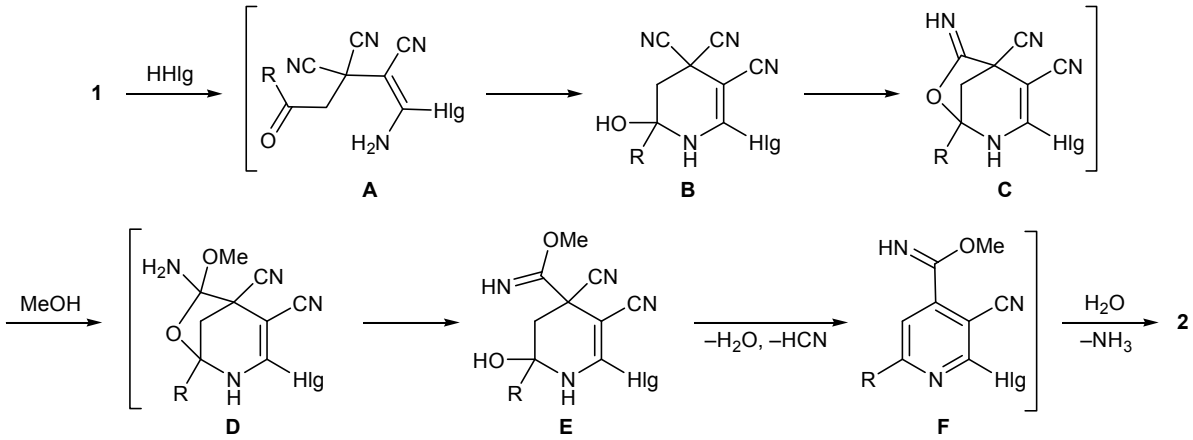
R = Me, Hlg = Cl (**a**), Br (**b**); R = *t*-Bu, Hlg = Cl (**c**).

Correlations in the HMBC spectrum of compound **2a**



^{1}H, δ, ppm	^{13}C, δ_C, ppm
7.95 (3-H)	164.68 (C^2), 162.34 (C^7), 105.51 (C^5), 24.15 (C^1)
3.95 (OC^{8}H$_3$)	162.34 (C^7)
2.63 (C^{1}H$_3$)	164.68 (C^2), 122.89 (C^3)

Scheme 2.



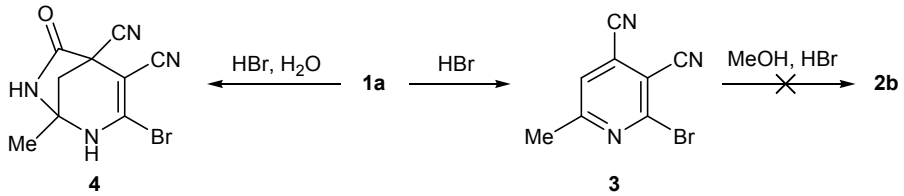
group is located in position *4* of the pyridine ring. In addition, the proton resonating at δ 7.95 ppm showed three more correlations, namely with C^2 (δ_C 164.68 ppm), C^5 (δ_C 105.51 ppm), and 2-CH_3 (δ_C 24.15 ppm). The methyl protons displayed couplings with the neighboring carbon atoms of the pyridine ring, C^2 and C^3 (δ_C 122.89 ppm). Protons of the ester methoxy group gave only one cross-peak with C^7.

Scheme 2 shows a probable mechanism of formation of compounds **2**. In the first step, addition of hydrogen halide to the terminal cyano group gives intermediate **A** which undergoes cyclization to tetrahydropyridine structure **B**. We previously isolated analogous hydroxytetrahydropyridine and determined its structure by X-ray analysis [6]. When the reaction was carried out in 1,4-dioxane or propan-2-ol, the next step was dehydrocyanation and dehydration with formation of 2-halopyridine-3,4-dicarbonitriles [3–5]. The use of methanol as solvent favors closure of lactone imine ring (intermediate **C**) via intramolecular interaction between spatially close hydroxy and cyano groups. The subsequent addition of a methanol molecule to **C** gives intermediate **D**. Analogous transformations were described previously for 3,3-diacetylcyclopropane-1,1,2,2-tetracarbonitrile [7]. Intermediate **D** is unstable and is converted to imidic ester **E** which undergoes aromatization as a result of elimination of water and hydrogen cyanide molecules. In the final step, hydrolysis of the imidic ester group in pyridine derivative **F** yields methyl 6-alkyl-3-cyano-2-halopyridine-4-carboxylate **2**.

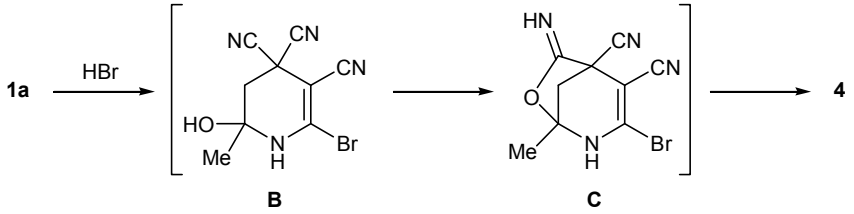
Alternative transformation sequences are also possible. For example, methyl ester **2** could be formed by reaction of 6-alkyl-2-halopyridine-3,4-dicarbonitrile **3** with methanol. In order to verify the proposed mechanism (Scheme 2) we performed additional studies. For this purpose, 4-oxopentane-1,1,2,2-tetracarbonitrile (**1a**) was reacted with hydrogen bromide and aqueous HBr in 1,4-dioxane. We thus obtained 2-bromo-6-methylpyridine-3,4-dicarbonitrile (**3**) and 3-bromo-1-methyl-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitrile (**4**), respectively. No ester **2b** was detected in the reactions of **3** with methanol in the presence of both dry hydrogen bromide and aqueous HBr (Scheme 3). The formation of compound **4** in the reaction of **1a** with HBr/H_2O (Scheme 4) may be regarded as an indirect evidence in support of Scheme 2. Intermediate **C** is converted to **4** via lactone imine–lactam rearrangement [4, 8, 9]. It should also be noted that the formation of methyl 6-alkyl-3-cyano-2-halopyridine-4-carboxylates **2** and 3-bromo-1-methyl-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitrile (**4**) involves intramolecular interaction of one cyano group with the carbonyl group [4].

The procedure proposed in this work for the synthesis of methyl 2-chloro-3-cyano-6-methylpyridine-4-

Scheme 3.



Scheme 4.



carboxylate (**2a**) is more advantageous than those described previously [10, 11] due to experimental simplicity and low number of steps. Pyridine derivatives **2a** and **2b** are convenient intermediate products for the synthesis of pyridoxine.

EXPERIMENTAL

The purity of the isolated compounds was checked by TLC on Sorbfil PTSKh-AF-A-UF plates; spots were visualized under UV light, by treatment with iodine vapor, or by thermal decomposition. The melting points were determined on an OptiMelt MPA100 melting point apparatus. The IR spectra were recorded in mineral oil on an FSM-1202 spectrometer with Fourier transform. The ^{1}H NMR spectra were measured on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were obtained on a Shimadzu GCMS-QP 2010 SE instrument.

Methyl 2-chloro-3-cyano-6-methylpyridine-4-carboxylate (2a). 4-Oxopentane-1,1,2,2-tetracarbonitrile, 0.005 mol, was dissolved in 5 mL of methanol, 5 mL of concentrated aqueous HCl was added with stirring, and the mixture was stirred for 1.5–3 h at 50°C. When the reaction was complete (TLC), the mixture was cooled and diluted with a 4–5-fold volume of water. The precipitate was filtered off and washed with water and propan-2-ol. Yield 0.86 g (82%), mp 116°C. IR spectrum, ν, cm^{-1}: 2235 (C≡N), 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 3.95 s (3H, OCH_3), 7.95 s (1H, 5-H). Mass spectrum: *m*/*z* 210/212 (I_{rel} 50/16%) $[M]^+$. Found, %: C 51.23; H 3.36; N 13.33. $C_9H_7ClN_2O_2$. Calculated, %: C 51.32; H 3.35; N 13.30. *M* 210.02.

Compounds **2b** and **2c** were synthesized in a similar way.

Methyl 2-bromo-3-cyano-6-methylpyridine-4-carboxylate (2b). Yield 0.97 g (76%), mp 106–107°C. IR spectrum, ν, cm^{-1}: 2231 (C≡N), 1732 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 3.94 s (3H, OCH_3), 7.96 s (1H, 5-H). Mass spectrum: *m*/*z* 254/256 (I_{rel} 32/31%) $[M]^+$. Found, %: C 42.23; H 2.76; N 11.05. $C_9H_7BrN_2O_2$. Calculated, %: C 42.38; H 2.77; N 10.98. *M* 253.97.

Methyl 6-*tert*-butyl-2-chloro-3-cyanopyridine-4-carboxylate (2c). Yield 0.97 g (77%), mp 103–104°C. IR spectrum, ν, cm^{-1}: 2233 (C≡N), 1736 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.34 s (9H, *t*-Bu), 3.96 s (3H, OCH_3), 7.97 s (1H, 5-H). Mass spectrum: *m*/*z* 252/254 (I_{rel} 11/3%) $[M]^+$. Found, %: C 57.09; H 5.16; N 11.08. $C_{12}H_{13}ClN_2O_2$. Calculated, %: C 57.04; H 5.19; N 11.09. *M* 252.07.

2-Bromo-6-methylpyridine-3,4-dicarbonitrile (3). 1,4-Dioxane was saturated with dry hydrogen bromide, 0.005 mol of 4-oxopentane-1,1,2,2-tetracarbonitrile was added, and the mixture was stirred for 1.5–3 h at 50–60°C. When the reaction was complete (TLC), the mixture was cooled and diluted with a 4–5-fold volume of water. The precipitate was filtered off, washed with water, and dried in air. The dry product was dissolved in hot acetonitrile or ethyl acetate, the solution was filtered from undissolved impurities, and the filtrate was cooled and diluted with a 4–5-fold volume of water (acetonitrile solution) or with hexane (ethyl acetate solution). The precipitate was filtered off and washed with propan-2-ol. Yield 0.80 g (72%), mp 56–57°C. IR spectrum: ν 2230 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 8.02 s (1H, 5-H). Mass spectrum: *m*/*z* 221/223 (I_{rel} 54/55%) $[M]^+$. Found, %: C 43.29; H 1.87; N 18.82. $C_8H_4BrN_3$. Calculated, %: C 43.27; H 1.82; N 18.92. *M* 220.96.

3-Bromo-1-methyl-6-oxo-2,7-diazabicyclo[3.2.1]-oct-3-ene-4,5-dicarbonitrile (4). 4-Oxopentane-1,1,2,2-tetracarbonitrile, 0.005 mol, was dispersed in 5 mL of 1,4-dioxane, 5 mL of 40% aqueous HBr was added with stirring, and the mixture was stirred for 1.5–3 h at 70–80°C. When the reaction was complete (TLC), the mixture was cooled and diluted with a 4–5-fold volume of water. The precipitate was filtered off and washed with water and ethyl acetate. If necessary, the product was recrystallized from ethyl acetate or acetonitrile. Yield 1.05 g (79%), mp 256–257°C. IR spectrum, ν, cm^{-1}: 3223–3107 (NH), 2255 (C≡N),

2213 (C≡N), 1689 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.48 s (3H, CH_3), 2.15 d and 2.61 d (1H each, CH_2, J = 10 Hz), 9.17 s (1H, NH), 9.53 s (1H, NH). Mass spectrum: m/z 266/268 (I_{rel} 11/12%) $[M]^+$. Found, %: C 40.39; H 2.58; N 20.92. $C_9H_7BrN_4O$. Calculated, %: C 40.47; H 2.64; N 20.98. M 265.98.

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